

Q14  
wrel.

medium and isolating said polypeptide from said cell or said nutrient medium.--

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In the Figures

Please amend Figures 5, 11, 12 and 17 as indicated in red on the attached copies.

**REMARKS**

After the above amendments, Claims 78 - 89 are active.  
Reconsideration is respectfully requested.

Applicants wish to thank the Examiner for the helpful interview held in her office on August 13, 1996. The matters discussed at the interview are summarized and expanded upon in the following remarks.

The Examiner states that the claims have been renumbered in accordance with 37 CFR 1.126. Applicants note that they have used the appropriate numbers in the above-amended claims.

Applicants call attention to the fact that Claims 78 and 79 clarify that the polypeptides encoded by the claimed polynucleotides are continuous sequences of amino acids corresponding to sequences beginning at amino acid -21 or 1 of SEQ ID NO: 25 and continuing through to a final amino acid that is selected from amino acids 151 through 244 of SEQ ID NO: 25. In the amended claims, the structure of the polypeptide now contains a Y component in order to clarify that between the end points of X and Z, there is a continuous stretch of amino acids corresponding to the indicated portions of SEQ ID NO: 25. Applicants submit that the revised claims do not contain new matter; they simply clarify the claimed subject matter.

The Examiner has objected to the specification and claims on the basis that they fail to comply with 37 CFR §1.821(d) regarding reference to sequence listings. The specification and claims were reviewed to ensure that wherever there was a reference to a sequence, its sequence identification number was used. In the course of this review, it was determined that SEQ ID NOS: 24, 25, 26, and 27 should have contained leader sequences as shown in FIG. 11 and FIG. 12, respectively. Additionally, it was decided that a sequence listing for the sequence provided in FIG. 25 should have been included as well. Therefore, a revised sequence listing was prepared and is being submitted herewith. The specification and claims have been amended accordingly to include the SEQ ID NOS. at the appropriate locations in the specification. No new matter has been added by these changes. It is submitted that these amendments overcome the objection to the specification and the claims.

In order to ensure consistent usage of a single numbering system, Applicants have amended the specification to number the leader sequences with negative numbers and the first amino acids of the mature proteins as number 1. This is supported by the specification as filed on page 35, lines 11-16. Based on this numbering system, Applicants have amended several numbers in the specification by subtracting the number 21, which is the length of the leader sequence. Further, Applicants have amended Figures 11 and 12 to reflect the chosen numbering system. Again, this is supported by the specification at page 35, lines 11-16.

A few of the changes made by the above amendments to the specification warrant additional explanation. First, Applicants have amended page 17, line 2 of the specification to change "173" to "174." This is made for accuracy in view of the definition of MGDF-2 on page 35, line 20 of the specification. That definition refers to amino acids 22-195 of Figure 11, which is a sequence having  $195-21=174$  amino acids. Thus, there is no new matter.

Second, the changes made at page 35 in the definition of MGDF-3 involved subtracting 21 from 286 rather than from 289, to yield 265. This also necessitated a change on line 11 of page 35 from "268" to "265".

Applicants submit that this does not constitute new matter on the following basis. Figure 12 shows the number 289 on the right hand side of the last coding line; however, the last amino acid actually ends at position 286. The number 289 arises from counting the last 9 nucleotides as if they were three codons, but it is clear from Figure 12 that they are not. The error was inadvertent. Therefore, the Examiner is requested to approve entry of this amendment.

Third, Applicants have amended page 100 of the specification to add the relevant ATCC deposit number. Applicants submit with this response a copy of the ATCC deposit form relating to this deposit, which shows the deposit number.

The Examiner also expressed concerns regarding the correspondence between the amino acids in the Figures and those of the sequence listings. The above amendments to the specification and claims also address this issue. Again, no new matter has been introduced. The sequences on the new Sequence Listing are based on the specific sequences that were already identified in the specification as filed.

The Examiner states that the declaration filed under 37 CFR 1.63 in this case is defective because it does not contain a statement in accordance with 37 CFR 1.63(d) regarding the duty to disclose to the Office information defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application. Applicants point out that they did state in the declaration that they were aware of their duty to disclose all information known to them to be material to patentability as defined in 37 CFR 1.56. However, to streamline prosecution, Applicants are filing a substitute declaration with this response to address this issue and they request that this new declaration be entered into the file.

The descriptions of Figures 5 and 17 in the section entitled "The Brief Description of the Drawings" have been amended as requested to refer to the multiple subparts separately. Clean copies of Figures 5, 11, and 14 are being submitted herewith as the Examiner requested. The clean

copies of Figures 5 and 11 are marked in red to indicate the proposed changes discussed in this response.

The cross-reference to the prior filed related applications is amended to include a reference to U.S. Serial No. 08/221,768. The status of the three prior applications is current.

### Double Patenting Rejections

The Examiner has provisionally rejected Claims 67-77 for obviousness-type double patenting over Claims 36-44 of co-pending application serial number 08/252,628 (the '628 application). Applicants traverse this provisional rejection as explained below.

The Examiner states that the claims of the '628 application are directed to fragments of the nucleic acids of the copending claims, which fragments are allegedly not patentably distinct from the nucleic acid encoding the protein in its entirety. The Examiner's position seems to be that the invention of the claimed truncated MGDF molecules with biological activity is part of the same invention as native (i.e., full-length) TPO molecules with biological activity.

In general, for a prima facie case of obviousness-type double patenting to apply, the teachings sufficient to support the prior claimed subject matter (i.e., the full-length DNA) must have suggested the currently claimed subject matter (i.e., the truncated DNAs) to one of ordinary skill in the art. Applicants submit that in this case, one of ordinary skill could not have predicted that such a large amount of truncation- DNA corresponding to 88 to 181 amino acids (see Claim 78)- would result in a DNA encoding a protein that retained a biological activity in common with the native molecule. See Table 10, page 95, wherein it is shown that MGDF-11 (amino acids 1-163 of SEQ ID NO: 25) produced in *E. coli* has activity to produce platelets in mice. Although the activity is lower than the full-length CHO produced molecule (see Table 10), it is still significant, since such a degree of truncation of the protein would have been expected to abolish activity. As discussed with the Examiner, Applicants have amended the claims to state

that the polypeptides encoded by the claimed polynucleotides are those that have the activity of specifically promoting megakaryocyte growth or differentiation. This amendment is supported in the specification as filed on page 15, lines 3-6, and in Table 10. The amended claims fully embrace the arguments and evidence discussed herein. In summary, while a disclosure of full-length DNA encoding an active MGDF molecule might enable one to claim the full-length molecule and some related molecules having minimal truncation, the degree of truncation involved in the current claims goes well beyond the realm of the predictable in the protein art.

In support of their position, Applicants call the Examiner's attention to some judicial decisions that are relevant to the issue outlined above. First, in *Genentech Inc. v. The Wellcome Foundation Ltd.*, 31 USPQ2d 1161 (Fed. Cir. 1994) (Exhibit A of this Response), the C.A.F.C. dealt with the question of whether a truncated variant of tPA infringed a claim in a U.S. patent to "human" tPA. The variant, referred to as FE1X, was missing 81 amino acids as compared with natural human tPA and had two additional amino acid changes. The C.A.F.C. held that FE1X did not infringe the claim. The Court stated that the specification of the patent had several broad definitions of tPA but few examples of particular biologically active species. The broad definitions of tPA were thus considered by the Court to be "hopelessly overbroad" [*Genentech*, page 1168]. The Court also stated that there was no basis in the specification for determining which of a potentially infinite number of permutations of tPA, including truncations, were biologically active and which were not. One expert testified that the properties of the permutations were "totally unpredictable." [*Genentech*, page 1168]. The Court concluded that "[t]he determination of which permutations are operative would thus require undue experimentation. Thus, we are unwilling to say that the specification satisfies the enablement requirement of 35 U.S.C. §112 P.1 (1988) with respect to these broader definitions, or that the PTO could have relied on these definitions in issuing the patent." [*Genentech*, page 1168].

It is interesting to note that the instant application involves DNA encoding a truncated protein that is missing a minimum of 88 amino acids from the TPO molecule, very similar to the number of amino acids missing

(i.e., 81) from the tPA molecule in the above-described case. In fact, it can be said that in the present case, the level of unpredictability is even greater than the tPA situation, since TPO has a total of 332 amino acids and a molecule missing 88 amino acids means that **27%** of the molecule is missing, whereas tPA has a total of 527 amino acids and a molecule missing 81 amino acids means that only **15%** of the molecule was missing. In referring to the missing 81 amino acids along with the two additional amino acid changes, the C.A.F.C. stated that these changes led to a “dramatically different” structure [*Genentech*, page 1171]. On the basis of the “profound differences in structure and properties” (*Ibid.*, page 1172), the C.A.F.C. concluded that FE1X did not infringe the patent.

Although the present situation is not an infringement setting, the issues are closely related. In *Genentech*, it was held that a truncated protein, FE1X, is different enough not to infringe a claim to human tPA and a specification enabling the former did not enable the latter. Likewise, in this case, the claimed truncated DNAs, which encode active proteins, are believed to be patentably distinct from the full-length DNA, since the prior specification directed to the full-length DNA and protein does not describe or enable the truncated DNAs.

*Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 U.S.P.Q. 1016-1031 (Exhibit B) also supports the conclusion stated above. See page 1027 of this decision.

The Patent Office has issued a number of separate U.S. patents directed to truncated proteins based on previously known proteins. See for examples, the following:

(a) U.S. Patent 5,001,057 “Truncated Human IL-1 cDNA Sequences which Encode Biologically Active Human IL-1 Proteins” (Exhibit C).

(b) U.S. Patent 5,516,512 “N- and C-Terminal Truncation and Deletion Mutants of Human Interleukin-3” [Note: preferred are those missing amino acids 120-130, 120-133, 116-133 and 130-133; according to column 7, lines 26-27 and 33-35, it is surprising that the expressed truncation mutants have biological activity]. ” (Exhibit D).

(c) U.S. Patent 5,459,250 "Truncated Mammalian Growth Factor DNA Sequence" [Note: the truncated proteins have about 140 amino acids out of 176 amino acid residues in the native protein]. " (Exhibit E).

(d) U.S. Patent 5,185,259 "Truncated Human Tissue Plasminogen Activator" [Note: the claimed variant has amino acid residues 69-527 as compared to 1-527 in the native protein]. (Exhibit F).

The fact that a number of U.S. patents have been granted on truncations of known proteins (and/or the corresponding DNAs), as evidenced by the above patents, supports Applicants position in this case that the DNAs encoding truncated active molecules of the present claims are a separate invention (i.e., patentably distinct) from full-length (native) TPO.

The Examiner further states that a similar double-patenting rejection may also apply to the pending claims over the claims of co-pending serial number 08/321,488 (the '488 application). The Examiner has not provided any reasons for such a rejection because the application was not available to the Examiner. Applicants submit that a double patenting rejection over claims of the '488 application is not appropriate in this case for the following reason.

The claims of the '488 application are directed to mono-pegylated derivatives of a particular truncated mpl ligand protein having 163 amino acids in total. The present claims are all directed to polynucleotides. As the Examiner has recognized in her Restriction Requirement dated January 17, 1996, the derivatized polypeptides of this invention (Group V) are a distinct invention from the polynucleotides (Group II). Therefore, as discussed with the Examiner at the interview, Applicants submit that the pending claims are patentably distinct from the claims of the copending application serial number 08/321,488.

The Examiner states that she did not find certain documents included in the 1449 form submitted February 15, 1995 in application Serial No. 08/252,628. In response, applicants are herewith submitting copies of such references for consideration by the Examiner.

For the Examiner's convenience, Applicants are filing herewith a consolidated listing of references on a modified Form 1449. This listing contains all of the references cited in the related cases, which were referred to in the Information Disclosure Statements filed in this case previously. The Examiner is requested to review the listing and to sign it indicating her review. Copies of all of the cited publications have previously been submitted in related case U.S. Serial No. 08/252,628 and/or related cases.

#### Objections and Rejections under 35 U.S.C. §112

The Examiner objects to the specification as allegedly failing to provide proper antecedent basis for the limitation of a nucleic acid encoding a polypeptide having as its C-terminus an amino acid from 172 to 265 of Figure 11. Applicants note that they have amended these numbers to "151 through 244" by subtracting the number 21 (corresponding to the length of the signal peptide). This was done to ensure consistency with the chosen numbering system, as discussed above. Applicants traverse this objection on the following grounds.

It is clear from the specification that Applicants contemplated a variety of truncations of the full-length mpl-ligand molecule. See pages 36-37 of the specification. Some preferred examples of truncated molecules of the invention are disclosed at the top of page 37. The present claim limitation of amino acids 172 through 265 is supported by the first and fifth preferred examples given on page 37. Applicants submit that it is proper to base claim limitations on particular examples since they form part of the disclosure. Applicants have limited the present claims to a preferred subset of truncated species which is supported by the above-identified examples. Therefore, the objection to the specification should be withdrawn.

The Examiner further objects to the specification and rejects the claims under 35 U.S.C. §112, first paragraph for various reasons provided at page 5, line 24 through page 6, line 21 of the Office Action. With one exception (discussed below), Applicants have amended the claims as suggested by the Examiner to obviate these objections and rejections.



The Examiner states that the specification does not teach how to make host cells transformed with DNA without a vector. However, Applicants submit that it was known as of the filing date how to transform cells without a vector. A patent application need not teach, and preferably omits, that which is well known in the art. See *Spectra-Physics Inc. v. Coherent Inc.*, 3 USPQ2d 1737 (Fed. Cir. 1987). For example, U.S. Patent 4,870,009 (Exhibit G) teaches how to transform fertilized eggs with genes for hormones that are attached to a strong promoter DNA. There is no requirement for a vector for transforming the fertilized eggs. In other situations as well, transformation as well as expression may be accomplished by incorporation of the MGDF gene into a genome of a mammalian cell, thus resulting in expression without a vector. For these reasons, Claim 87 of the claims depends directly from Claim 81.

Applicants are filing a Petition under 37 CFR §1.48(b)(1) in order to delete inventors who did not make contributions to the currently pending claims. The change in inventorship was necessitated by the cancellation of previously active claims. Inventorship was correctly given for the application as filed.

In light of the above amendments and remarks, Applicants submit that this application is now in condition for further consideration and allowance, and an early notice to that effect is earnestly requested.

Respectfully submitted,



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Date: 11/26/96

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M/S 10-1-F  
AMGEN INC.  
Amgen Center  
1840 Dehavilland Drive  
Thousand Oaks, California 91320-1789



CORRECTED

# American Type Culture Collection

12301 Parklawn Drive • Rockville, MD 20852 USA • Telephone: (301)231-5520 Telex: 898-055 ATCCNORTH • FAX: 301-770-2587

## BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

### INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3  
AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

To: (Name and Address of Depositor or Attorney)

Amgen, Inc.  
Attn: George W. Stearns  
Amgen Center  
1840 Dehavilland Drive  
Thousand Oaks, CA 91320-1789

Deposited on Behalf of: Amgen, Inc.

Identification Reference by Depositor:

ATCC Designation

*E. coli* cells, strain K12/FM15

69717

The deposit was accompanied by: ☐ a scientific description ☒ a proposed taxonomic description indicated above.

The deposit was received November 30, 1994 by this International Depository Authority and has been accepted.

### AT YOUR REQUEST:

☒ We will inform you of requests for the strain for 30 years.

The strain will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strain and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strain.

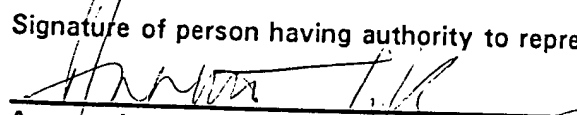
If the culture should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace it with living culture of the same.

The strain will be maintained for a period of at least 30 years after the date of deposit, and for a period of at least five years after the most recent request for a sample. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the culture cited above was tested December 20, 1994. On that date, the culture was viable.

International Depository Authority: American Type Culture Collection, Rockville, Md. 20852 USA

Signature of person having authority to represent ATCC:

  
Annette L. Bade, Director, Patent Depository

Date: December 21, 1994

C4 RP-HPLC Purification of Mpl Ligand  
Sample = Superdex 200 Fraction 42

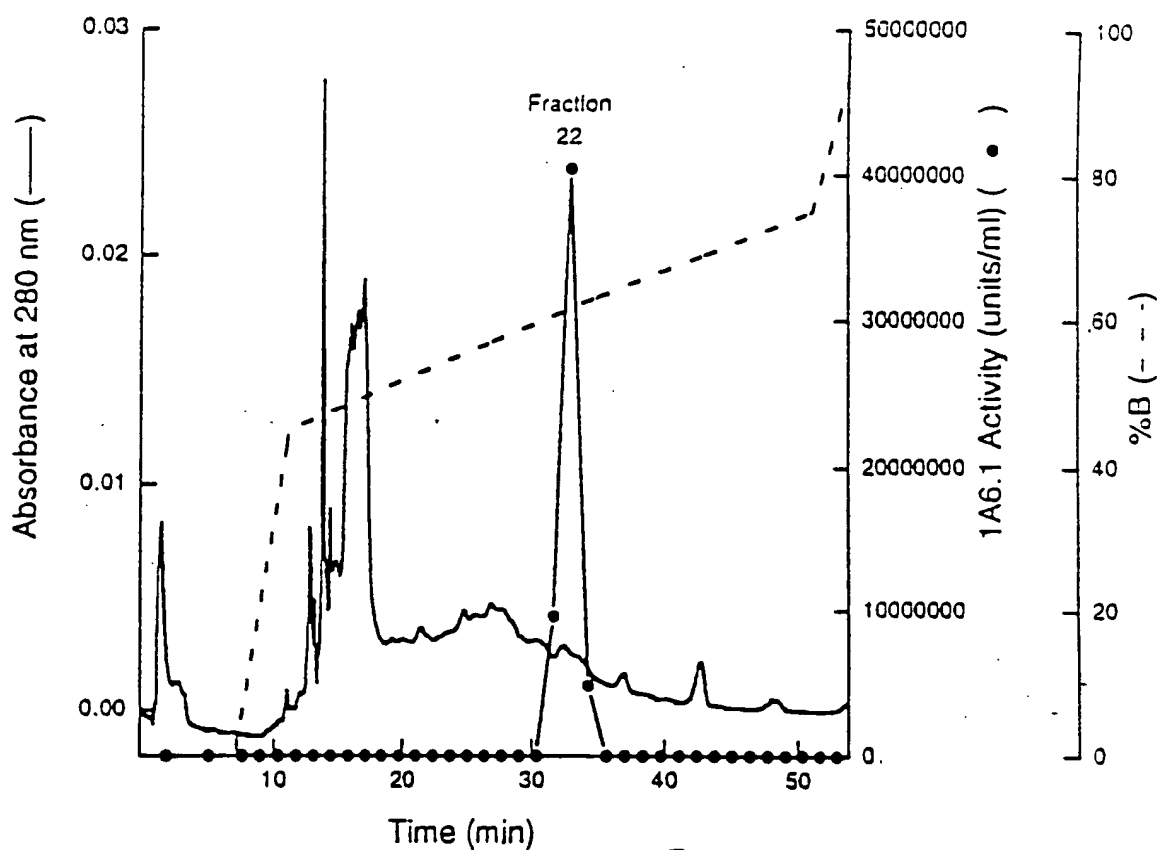
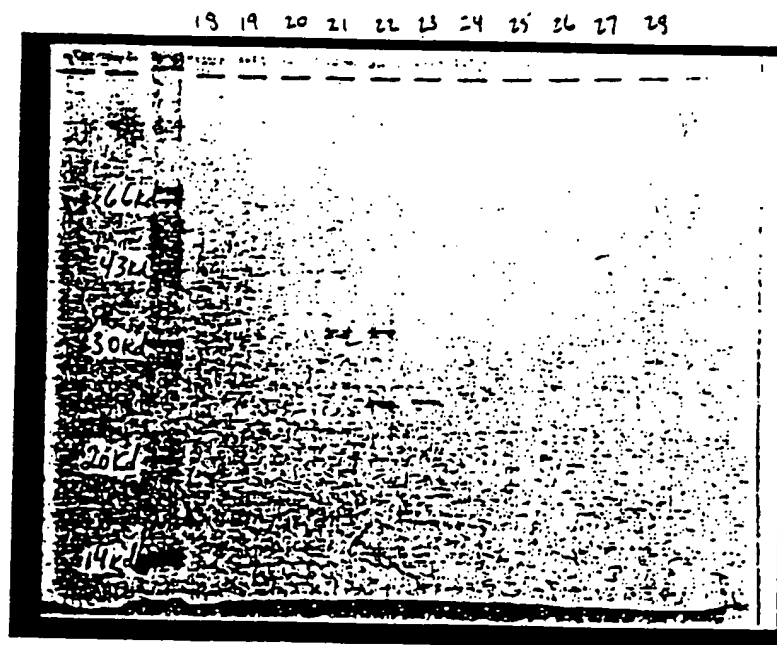


FIG. 5A



SDS-PAGE 14% NONREDUCING

Figure 5

FIG. 5B

## MDGE-1

	-21	1	CAGGGAGCCACGCCAGGCAAGCACCCCCCGCAGATGGAGGTGACTGAATTGCCTC	59
			MecGluLeuThrGluLeuLeuLeu	8-14
	-13	60	GTCGTCATGCTTCTCTTAAGTGAAAGGTTAAGCCTGTCCAGCCCAGCTCTCTCTGTTOT	119
			ValValMecLeuLeuLeuThrAlaArgLeuThrLeuSerSerProAlaPProAlaCys	287
	8	120	GACCTCCGAGTCTCATATAACTGCTTCTGACTCCCATGTCTTCACAGCAGACTGAGC	179
			AspLeuArgValLeuSerLysLeuLeuArgAspSerHisValLeuHisSerArgLeuSer	4827
	28	180	CAGTCCCCAGAGGTTACCCTTTGCCACACCTGTCTCTGCTGCTGCTGCTGCTGCTTAGC	239
			GlnCysProGluValHisProLeuProThrsProValLeuLeuProAlaValAspPheSer	5847
	48	240	TTCGGAGAATGGAAAACCCAGATGGAGGAGACAAGGCACAGGACATTCTGGGAGCAGTG	299
			LeuGlyGluTrpLysThrGlnMecGluGluThrLysAlaGlnAspIleLeuGlyAlaVal	8867
	68	300	ACCTTCTCTGTCAGGGAGTGATGGCAGCAGGGGACAAGTGGGAGCCACTTGCTCTCA	359
			ThrLeuLeuLeuGluGlyValMetAlaAlaArgGlyGlnLeuGlyProThrCysLeuSer	10887
	88	360	TCCCTCTCTGGGACAGCTTCTGGACAGTCCCTCTCTCTCTTGGGGCCCTGCAGAGCCTC	419
			SerLeuLeuGlyGlnLeuSerGlyGlnValArgLeuLeuLeuGlyAlaLeuGlnSerLeu	128107
	108	420	CTTGGAACCCAGCTTCTCTCAAGGCGAGGACACAGCTCACAGGATCCCATGGCATC	479
			LeuGlyThrGlnLeuProProGlnGlyArgThrThrAlaHisLysAspProAsnAlaIle	148127
	128	480	TTCCTGAGCTTCCAACACCTGCTCCGAGGAAGGTGCTTTCTCATGCTTGTAGGAGGG	539
			PheLeuSerPheGlnHisLeuLeuArgGlyLysValArgPheLeuMecLeuValGlyGly	168147
	148	540	TCCACCTCTGCTCAGGCGGGGGGGGCCACCCACAGGTGTCCCGAGCAGACCTCTCTA	599
			SerThrLeuCysValArgArgAlaProProThrThrAlaValProSerArgThrSerLeu	188167
	168	600	GTCTCACACTGAACGAGCTCCCAAACAGGACTTCTGGATTCTTGGAGCAAACTTCACT	659
			ValLeuThrLeuAsnGluLeuProAsnArgThrSerGlyLeuLeuGluThrAsnPheThr	208187
	188	660	GCCTCAGCCAGACTACTGAGCTCTGGGCTTCTGAGTGGCAGCAGGGATTGAGGCCAG	719
			AlaSerAlaArgThrThrGlySerGlyLeuLeuLysTrpGlnGlnGlyPheArgAlaLys	228207
	208	720	ATTCTGTGCTCTGAACAAACCTCCAGTCCCTGGACAAATCCCCGGATACCTGAC	779
			IleProGlyLeuLeuAsnGlnThrSerArgSerLeuAspGlnIleProGlyTyrLeuAsn	248227
	228	780	AGGATACAGAACTCTTGAATGGAACTCTGGACTCTTCTCGACCTCAGCAGGACC	839
			ArgIleHisGluLeuLeuAsnGlyThrArgGlyLeuPheProGlyProSerArgArgThr	258247
	248	840	CDGGAGCCCCGACATTCTCTGAGAACATGACACAGGCTCCCTGCCACCCACCTC	899
			LeuGlyAlaProAspIleSerSerGlyThrSerAspThrGlySerLeuProProAsnLeu	288267
	268	900	CAGCTGGATATCTCTCTTCCCACCCATCTCTCTACTGGACGTATACCTCTTCTCT	959
			GlnProGlyTyrSerProSerProThrHisProProThrGlyGlnTyrThrLeuPhePro	308287
	288	960	CTTCCACCCACTTCCCAACCTGTGTTCAGCTCCACCCCTCTCTCTGACCTTCT	1019
			LeuProProThrLeuProThrProValValGlnLeuHisProLeuLeuProAspProSer	328307
	308	1020	GCTCCAGCCCAACCTTACCAGCCCTCTCTTAACACATCTACACCCACTCCAGAT	1079
			AlaProThrProThrProThrSerProLeuLeuAsnThrSerTyrThrHisSerGlnAsn	348327
	328	1080	CTGTCTCAGGAGGTTAGTTCTTCACTGCGACTCCCGATCAGCATGTCTCTGTGACG	1139
			LeuSerGlnGluGlyIle	353332
		1140	CTCCTCTCTGGAGGGGCCCCCTGGGAGCACTGGCAGATTTCCTACTTTCTCTCTG	1199
			AACCCCAAGCCCTGTAAAGGGATACAGGACTGAAGGGAATCATTITTAAGTGT	1259
		1200	ACATTATAAGCTTCAGAGCTATTTTTAAGTATACCAACTCATACAGGAGCT	1319
		1260	AGCTCTTTGCTCATTTCTGCA	1342

**Figure 11**

## Human MDGF cDNA (no IVS 5)

1	AGGGAGCCACCCAGCCAGACACCCCCGCCAGATGGAGCTGACTGAATTGCTCCTCGTG	60
-21	MetGluLeuThrGluLeuLeuLeuVal	9-13
61	GTCATGCTTCTCCTAACTGCAAGGCTAACGCTGTCCAGCCCCGGCTCCTCTGCTTGTGAC	120
-12	ValMetLeuLeuLeuThrAlaArgLeuThrLeuSerSerPProAlaPProProAlaCysAsp	29-8
121	CTCCGAGTCTCCTCAGTAAACTGCTTCGTGACTCCCATGTCTTTCACAGCAGACTGAGCCAG	180
9	LeuArgValLeuSerLysLeuLeuArgAspSerHisValLeuHisSerArgLeuSerGln	49-28
181	TGCCCAGAGGTTACCCCTTTGGCTACACCTGTCTGTGCTGCTGTGGACTTTAGCTTG	240
29	CysPProGluValHisPProLeuPProThrPProValLeuLeuPProAlaValAspPheSerLeu	69-48
241	GGAGAATGGAAACCCAGATGGAGGAGACCAAGGCACAGGACATTCTGGGAGCAGTGACC	300
49	GlyGluTrpLysThrGlnMetGluGluThrLysAlaGlnAspIleLeuGlyAlaValThr	89-68
301	CTTCTGCTGGAGGGAGTGATGGCAGCACGGGCAACTGGGACCCACTTGCCTCTCATCC	360
69	LeuLeuLeuGluGlyValMetAlaAlaArgGlyGlnLeuGlyPProThrCysLeuSerSer	109-88
361	CTCCTGGGGCAGCTTTCTGGCAGGTCCCTCTCCTCCTTGGGGCCCTGCAGAGCTCCTT	420
89	LeuLeuGlyGlnLeuSerGlyGlnValArgLeuLeuLeuGlyAlaLeuGlnSerLeuLeu	129-168
421	GGAAACCAGCTTCTCCACAGGGCAGGCCACAGCTCACAAGGATCCCAATGCCATCTTC	480
109	GlyThrGlnLeuPProProGlnGlyArgThrThrAlaHisLysAspPProAsnAlaIlePhe	149-128
481	CTGAGCTTCCACACCTGCTCCGAGGAAAGGACTTCTGGATTGTTGGAGCAAACCTTCAC	540
129	LeuSerPheGlnHisLeuLeuArgGlyLysAspPheTrpIleValGlyAspLysLeuHis	169-148
541	TGCCCTAGCCAGACTACTGGCTCTGGGCTTCTGAAGTGGCAGGAGGGATTACAGCCAA	600
149	CysLeuSerGlnAsnTyrTrpLeuTrpAlaSerGluValAlaAlaGlyIleGlnSerGln	189-168
601	GATTCCTGGTCTGCTGAACCAACCTCCAGGTCCCTGGACCAAAATCCCGGATACCTGAA	660
169	AspSerTrpSerAlaGluPProAsnLeuGlnValPProGlyPProAsnPProArgIlePProGlu	209-188
661	CAGGATACAGAACTCTTGAATGGAATCTGTGACTCTTTCTGGACCTCAGCCAGGAC	720
189	GlnAspThrArgThrLeuGluTrpAsnSerTrpThrLeuSerTrpThrLeuThrGlnAsp	229-208
721	CCTAGGAGCCCCGGACATTTCTCAGGACATCAGACACAGGCTCCCTGCCACCCAACTT	780
209	PProArgSerPProGlyHisPheLeuArgAsnIleArgHisArgLeuPProAlaThrGlnPPro	249-228
781	CCAGCTGGATATCTCTCTTCCCAACCCATCTCTACTGGACAGTATACGCTCTTCCC	840
229	PProAlaTrpIlePheSerPhePProAsnPProSerSerTyrTrpThrValTyrAlaLeuPPro	269-248
841	TCTTCCACCCAACTTGGCCACCCCTGTGGTCCAGCTCCACCCCTGCTTCTGACCTTTC	900
249	SerSerThrHisLeuAlaHisPProCysGlyPProAlaPProPProPProAlaSerIle	289-265
901	TGCTCCACGCCCCCCTACCGCCCTCTTCTAAACATCTTACCCCACTCCACGAA	960
961	TCTGTCTCAGGAGGTTAGTTCTCTGACACTGCCGACATCAGCAATTGCTCTGTGACA	1020
1021	GCTCCTTCTCTCCAGGCCCCCTGGGACACACTGGACAGATTCTCTACTTTCTCT	1080
1081	GAAACCCAAAGCCTGTGTAAAGGGATACAGGACTGAAAGGGATCATTTTCTACTG	1140
1141	TACATTATAACCTTCAGAGCTA 1164	

**Figure 12**

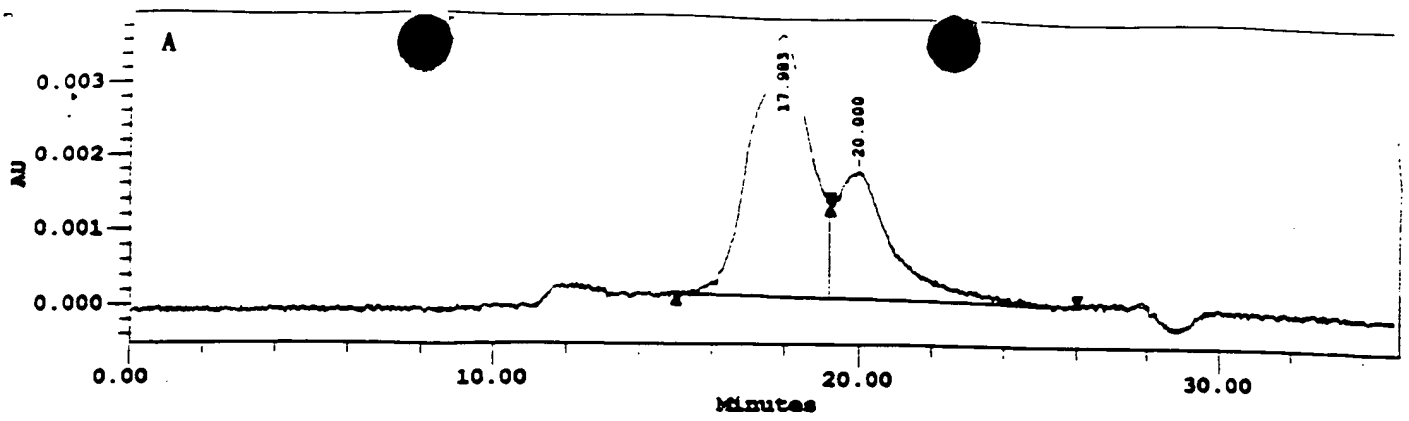


FIG. 17A

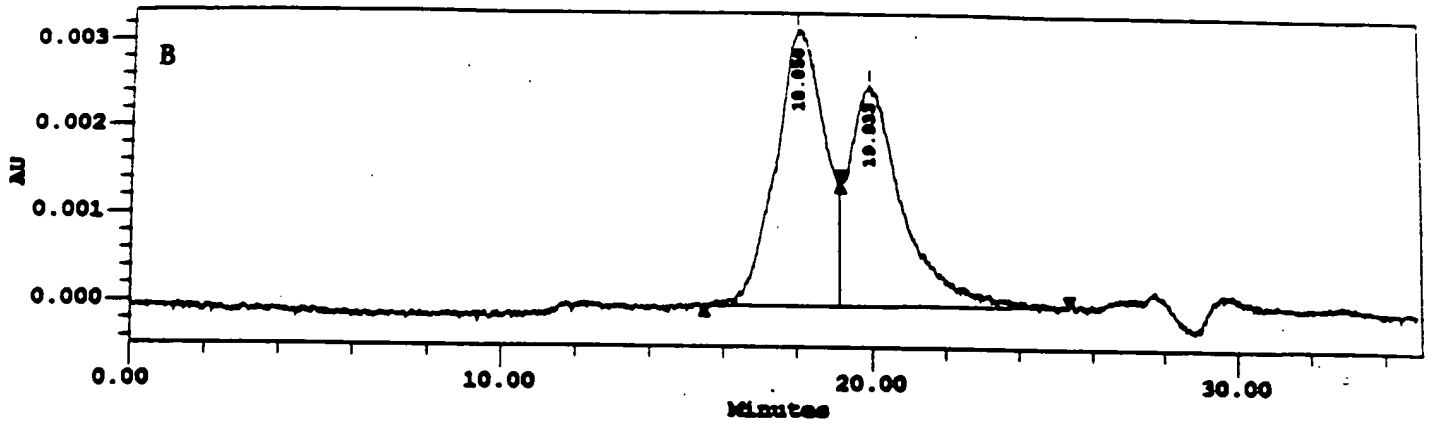


FIG. 17B

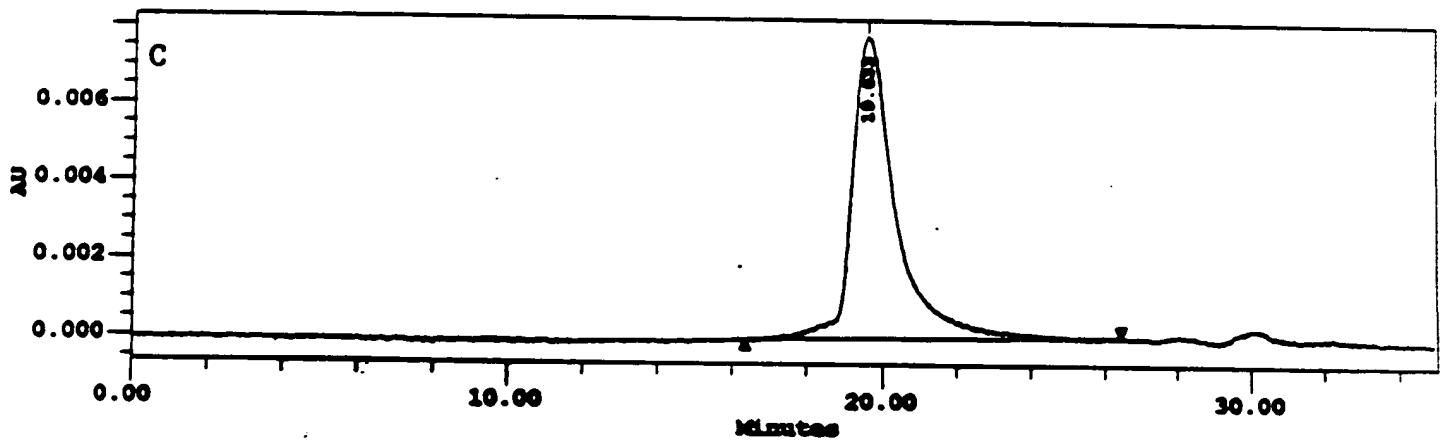


FIG. 17C

Figure 17